FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF AMBRISENTAN BY DIRECT COMPRESSION METHOD.

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: THATIPETA S G SREENIVASAN

REG.No. 261610262

Under the Guidance of

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CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF AMBRISENTAN BY DIRECT COMPRESSION METHOD",** submitted by the student bearing **Reg. No: 261610262** to "**The Tamil Nadu Dr. M.G.R. Medical University – Chennai**", in partial fulfilment for the award of Degree of **Master of Pharmacy** in **Pharmaceutics** was evaluated by us during the examination held on.....

Internal Examiner **External Examiner**

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DECLARATON

I do hereby declared that the dissertation **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF IMMEDIATE RELEASE TABLETS OF AMBRISENTAN BY DIRECT COMPRESSION METHOD"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2017-2018, under the guidance and supervision of **Mr. C. Kannan, M.Pharm.,** Assistant Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam **Mr. THATIPETA S G SREENIVASAN**

Date: **Reg.no. 261610262**

Dedicated to Parents,

Teachers&

My Family

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1. INTRODUCTION

Oral route is most popular for systemic effect due to its easy of ingestion, pain avoidance, versatility and most importantly patient compliance. Solid oral delivery systems (especially tablets) is system of choice among all drug delivery system and they do not require special treatment and are therefore less expensive to manufacture, likewise immediate release tablets are more acceptable among all the tablets. Based on their drug-release characteristics, tablets can be classified into three types, immediate release, extended release and delayed release. For immediate release tablets the drug is intended to be released rapidly after administration, or the tablet is dissolved and administered as a solution. This is the most common type of tablet and includes disintegrating, chewable, effervescent, sublingual and buccal tablets. They design to disintegrate and release their medication with no special rate controlling features. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques. In pharmaceutical industries, manufactures of generic tablets are usually focused on the optimization of the excipients mixture composition to obtain a product that meet established standard[1].

An ideal dosage regimen in the drug therapy of any disease or the goal of any drug delivery system is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration treatment.

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Immediate release drug delivery systems are designed to provide immediate drug levels in short period of time. In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms considering

quality of life, most of these efforts have been focused on ease of medication.

At present novel drug delivery systems are developed for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance. In these solid formulations do not require sterile conditions and are therefore, less expensive to manufacture[32].

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patientcompliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. Superdisintegrants are first choice of excipients which are extensively used for the formulation development of the immediate release tablets as they effectively result into the immediate disintegration, release and absorption of the drug after administration into the body.

1.1 Introduction to Solid Oral Dosage Forms:

Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing; Sometimes immediate onset of action is required than conventional therapy in many cases. Tablets are the most popular dosage form because of its unique properties such as ease of administration, low cost and non-invasive therapy etc.Therapeutic success of any therapy depends on the patient's compliance toward the therapy. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form.

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tableting, disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste, and pigments to make the tablets visually attractive. Apolymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered sublingually, buccally, rectally or intra vaginally. The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. Medicinal tablets were originally made in the shape of a disk of whatever color their components determined, but are now made in many shapes and colors to help distinguish different medicines. Tablets are often stamped with symbols, letters, and numbers, which enable them to be identified. Sizes of tablets to be swallowed range from a few millimeters to about a centimeter.

1.2. Types and Classes of Tablet: [4,5]

A. Oral Tablets for Ingestion:

1. Compressed tablets
2. Multiple compressed tablets
3. Layered tablets
4. Compression-coated tablets
5. Repeat-action tablets
6. Delayed-action and enteric-coated tablets
7. Sugar and chocolate-coated tablets
8. Film coated tablets
9. Chewable tablets

B. Tablets Used in the Oral Cavity: [4,5]

1. Buccal tablets
2. Sublingual tablets
3. Troches and lozenges
4. Dental cones

C. Tablets Administered by Other Routes: [4,5]

1. Implantation tablets
2. Vaginal tablets

D. Tablets Used to Prepare Solutions: [4,5]

1. Effervescent tablets
2. Dispensing tablets
3. Hypodermic tablets
4. Tablet triturates

1.3 Introduction to Immediate Release Tablets:[6]

Definition: Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. The term "release" includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. It also finds applications in the field of local delivery of drug to the stomach and proximal small intestine and importantly in treating microorganisms (Helicobacter pylori).

In immediate release tablets, disintegration is one of the important parameter. With the help of design of experiment (DOE) approach, process variables are first 'screened' to determine which are important to the outcome (excipients type, percentage, disintegration time (DT), etc. Next step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture. Immediate release tablets have gained prominence of being new drug delivery systems. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic.

Immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time.

Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat unwanted defect or disease[30].

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially as Croscarmellose sodium, Crospovidone and SSG[31].

1.4.DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM:

1.4.1. Ideal Properties[5]

Immediate release dosage form should

1. It should dissolve or disintegrate in the stomach within a short period In the case of solid dosage.
2. Should show first absorption and dissolution of drug.
3. Rapid onset of action always seen with immediate release tablets.
4. Must be compatible with taste masking.
5. Be portable without fragility concern.
6. It should not leave minimal or no residue in the mouth after oral administration.
7. Provides pleasing mouth feel.
8. Exhibit low sensitivity to environmental condition as humidity and temperature.
9. Be manufactured using conventional processing and packaging equipment at low cost.

1.4.2.Advantages[2,3]

An immediate release pharmaceutical preparation offers

1. Improved stability, bioavailability.
2. Decreased disintegration and dissolution times for immediate release oral dosage forms.

3. Suitable for controlled, sustained release actives.
4. High drug loading is possible.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging machinery.
7. Cost- effective.
8. Improved compliance added convenience.
9. Accurate dose: The immediate/fast dissolve dosage forms have the added advantages of convenience and accurate dosing as compared to liquids.
10. Ease of swallowing is possible.
11. Bilayer tablet is possible for sequential release of two drugs in combination and separate two incompatible substance.

1.4.3.Disadvantage[2][3]

1. Possess swallowing difficulty.
2. Onset of action is slow and depends on disintegration and dissolution. Some drugs resist compression, due to their amorphous nature or low-density
3. Drugs having bitter taste, objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating of tablet.
4. Drug release at a time may produce high plasma concentration which may produce toxicity.
5. Frequent dosing is necessary for drug with short half-life.

1.4.4.Salient Features

- Drugs should possessing long biological half-life for immediate release drug delivery.
- The drug is released quickly and completely in one shot.
- High bioavailability expected with immediate release dosage form.
- Lower clearance and lower elimination half-life are also requirement for immediate release drug delivery system.

- But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat unwanted defect or disease.
- Rapid drug therapy intervention is possible.
- New business opportunities like product differentiation, line extension and lifecycle management, exclusively of product promotion.

1.5.Criteria for Drug Selection

- Poor solubility of the drug and need immediate drug action in case of immediate release dosage form.
- The immediate release compositions comprise micronized drug in an amount sufficient to provide the desired daily dosage, that is, an amount of about 10 mg to about 1000 mg, more preferably an amount of about 20 mg to 400 mg.
- Immediate release compositions from which about 50% of the micronized drug is dissolved in vitro within about 15 minutes, more preferably at least about 80% of the drug is dissolved in vitro within about 30 minutes.
- Carrier materials for immediate release compositions preferably are selected to provide a disintegration time less than about 30 minutes, preferably about 20 minutes or less, more preferably about 18 minutes or less.

1.6.Unsuitable drug characteristic for immediate release tablets:

- Drug are not suitable for immediate release tablets which having short biological half-life.
- Drug with low bioavailability are also not desirable candidate for immediate release tablets.
    - Drug with higher clearance and higher elimination half-life are also not desirable candidate for immediate release tablets.

1.7.Pharmacokinetics:[6]

In this consideration, study has done on absorption, distribution, metabolism and excretion. After absorption, drug attains therapeutic level and therefore elicits pharmacological effect, so bothrate and extend of absorption is important. In conventional dosage form there is delay in disintegration and therefore dissolution is fast. Drug distribution depends on many factors like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces thebiotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

1.8.Pharmacodynamics:[6]

Drug reception interaction impaired in elderly as well as in young adult due to undue development of organ.

1. Decreased ability of the body to respond reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin. Immunity is less and taken into consideration while administered antibiotics
2. Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates
3. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.

1.9.Technology for Immediate release Tablets[6]

Conventional Techniques

Conventional technique used in the preparation of immediate release tablets

- ✓ Tablet molding technique
- ✓ Direct compression technique
- ✓ Granulation technique
- ✓ Mass extrusion technique

Several Technologies are available to manufacture immediate release tablets. The most common preparation methods are molding, lyophilisation or freeze drying, direct compression, spray drying and sublimation.

A. Tablet molding technique[4] [6]

Water-soluble ingredients are used in tablet molding technique which facilitate tablet to disintegrate and dissolve rapidly. A hydro alcoholic solvent use to moisten powder blend and is molded in to tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Two problems commonly encountered are mechanical strength and poor taste masking characteristics in this technique.

B. Direct compression technique[4] [6]

The term “direct compression” is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pre-treatment of the powder blend by wet or dry granulation procedure is required. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression, thus offering advantage particularly in terms of speedy production, as it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

Advantages[6]

1. Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
2. The most important advantage of direct compression is that it is an economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipment's is required, less process validation, reduced consumption of power.
3. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API.
4. Particle size uniformity.
5. Prime particle dissolution.

In case of directly compressed tablets after disintegration each primary drug particle is liberated. While in the case of tablets prepared by compression of granules small drug particles with a larger surface area adhere together into larger agglomerates, thus decreasing the surface area available for dissolution.

Disadvantages

a) Excipients Related[6]

1. Problems in the uniform distribution of low dose drugs.
2. High dose drugs having high bulk volume, poor compressibility and poor flow ability are not suitable for direct compression for example, Aluminum Hydroxide, Magnesium Hydroxide.
3. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.
4. Many active ingredients are not compressible either in crystalline or amorphous forms.

b) PROCESS Related [7]

1. Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
2. In some case it requires greater sophistication in blending and compression equipment's.

C. Granulation technique[4]

Granulation may be defined as a size enlargement process which converts small particles into physically stronger &larger agglomerates. The objective of granulation is to improve powder flow and handling, decrease dustiness, and prevent segregation of the constituents.

Granulation method can be broadly classified into two types

(i) Wet granulation[4]

(ii) Dry granulation[4]

Ideal characteristics of granules

The ideal characteristics of granules include spherical shape, smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness etc.

The effectiveness of granulation depends on the following properties:

- Particle size of the drug and excipients
- Type of binder (strong or weak)
- Volume of binder (less or more)
- Wet massing time (less or more)
- Amount of shear applied
- Drying rate (Hydrate formation and polymorphism)

(i) Wet granulation[4]

Wet granulation is a commonly used unit operation in the pharmaceutical industry. Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over-wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables.

Important steps involved in wet granulation

- Mixing of drug(s) and excipients.
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Course screening of wet mass using a suitable sieve (6-12 screens).
- Drying of moist granules.
- Screening of dry granules through a suitable sieve (14-20 screen).
- Mixing of screened granules with disintegrant, glidant, and lubricant.(Manish

Limitation of wet granulation[4]

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- Loss of material during various stages of processing.
- Stability may be a major concern for moisture sensitive or thermolabile drugs.
- An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

1.10.Special wet granulation techniques

- High shear mixture granulation
- Fluid bed granulation
- Extrusion-spheronization
- Spray drying

(ii) Dry granulation[4]

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules.

Two methods are used for dry granulation.The more widely used method is slugging, where the powder is precompressed and the resulting tablets or slugs are milled to yield granules.The other method is to precompress the powder with pressure rolls using a machine such as Chilosonator.

Advantages

The main advantages of dry granulation or slugging are that it uses less equipment's and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation.

Slugging can be used for advantages in the following situations

- For moisture sensitive material
- For heat sensitive material
- For improved disintegration since powder particles are not bonded together by a binder.

Disadvantages

- It requires a specialized heavy duty tablet press to form slug.
- It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
- The process tends to create more dust than wet granulation, increasing the potential contamination.

Steps in dry granulation

1. Milling of drugs and excipients
2. Mixing of milled powders
3. Compression into large, hard tablets to make slug
4. Screening of slugs
5. Mixing with lubricant and disintegrating agent
6. Tablet compression

Two main dry granulation processes

a) Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b) Roller compaction

The compaction of powder by means of pressure roll can also be accomplished by a machine called Chilosonator. Unlike tablet machine, the Chilosonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

D. Mass-Extrusion technique

Here softening of active blend done with solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. In case of bitter drug granules can be coated with the help of dried cylinder to achieve taste masking.

Solid dispersions method:

The immediate release dosage forms containing a solid dispersion that enhances the Solubility of a "low-solubility drug," meaning that the drug may be either "substantially Water-insoluble," which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, "sparingly water-soluble," that is, has an aqueous solubility up to about 1to2 mg/mL, or even low to moderate aqueous- solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/ml.

1.11.Few therapeutical area uses in the formulation of immediate release dosage form[33]:

1. **Analgesics and Anti-inflammatory Agents:** Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamicacid, Nabumetone, Oxyphenbutazone.
2. **Anthelmintics:** Albendazole, Mebendazole, Oxantel, Embonate, Embonate, Thiabendazole.
3. **Anti-Arrhythmic Agents:** Amiodarone Hcl, Disopyramide.
4. **Anti-bacterial Agents:** Penicillin, Ciprofloxacin HCl, Clarithromycin, Clofazimine, Doxycycline, Erythromycin, Nalidixic Acid, Nitrofurantoin, Rifampicin, Sulphabenzamide, Sulphamethoxazole, Sulphapyridine, Trimethoprim.
5. **Anti-coagulants:** Dicoumarol, Dipyridamole.
6. **Anti-depressants:** Amoxapine, Ciclazindol, Maprotiline HCl, Mianserin HCl,Trazodone HCl.
7. **Histamine H,-Receptor Antagonists**: cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl.
8. **Anti-diabetics:** Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide.
9. **Anti-hypertensive Agents:** Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem HCl, Diazoxide, Guanabenz Acetate,

Indoramin, Isradipine, Minoxidil, Nicardipine HCl, Nifedipine, Nimodipine, Reserpine.

10. **Gastro-intestinal Agents:** cimetidine, cisapride, diphenoxylate HCl,famotidine, loperamide, mesalazine, nizatidine, omeprazole.
11. **Diuretics:** Acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene.
12. **Cardiac Inotropic Agents:** Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.
13. **Anxiolytic, Sedatives, Hypnotics and Neuroleptics:** Etizolam, Alprazolam, Amylobarbitone, Barbitone, Bentazepam, Bromazepam, Bromperidol, Brotizolam, Chlormethiazole, Chlorpromazine, Diazepam, Droperidol.
14. **Histamine H,-Receptor Antagonists:** Acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadine HCl, dimenhydrinate, flunarizine HCl.

1.12.DISINTEGRANTS:

Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1- 10 % by weight relative to the total weight of the dosage unit. Diverse categories of Superdisintegrants such as synthetic, semi-synthetic, natural and co-processed blends etc. have been employed to develop effective immediate release tablets and to overcome the limitations of conventional tablet dosage form.[36]

They promote moisture penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared. Most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth. Most prior studies have focused on the function related properties of superdisintegrants with

special emphasis on correlating these functional properties to disintegrant efficiency and drug release rate.[37]

1.13.MECHANISM OF DISINTEGRATION BY SUPERDISINTEGRANTS:

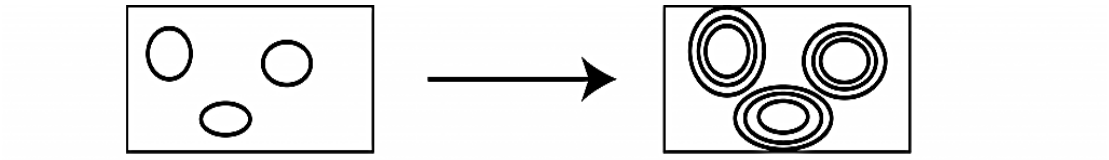
There are five major mechanisms for tablet disintegration as follows:-

1) Swelling
2) Porosity and Capillary Action (Wicking)
3) Deformation
4) Due to disintegrating particle/particle repulsive forces
5) Enzymatic reaction

1. **Swelling:**

Swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart. E.g Sodium starch Glycolate.[38]

Fig.1. Swelling of granules due to superdisintegrants

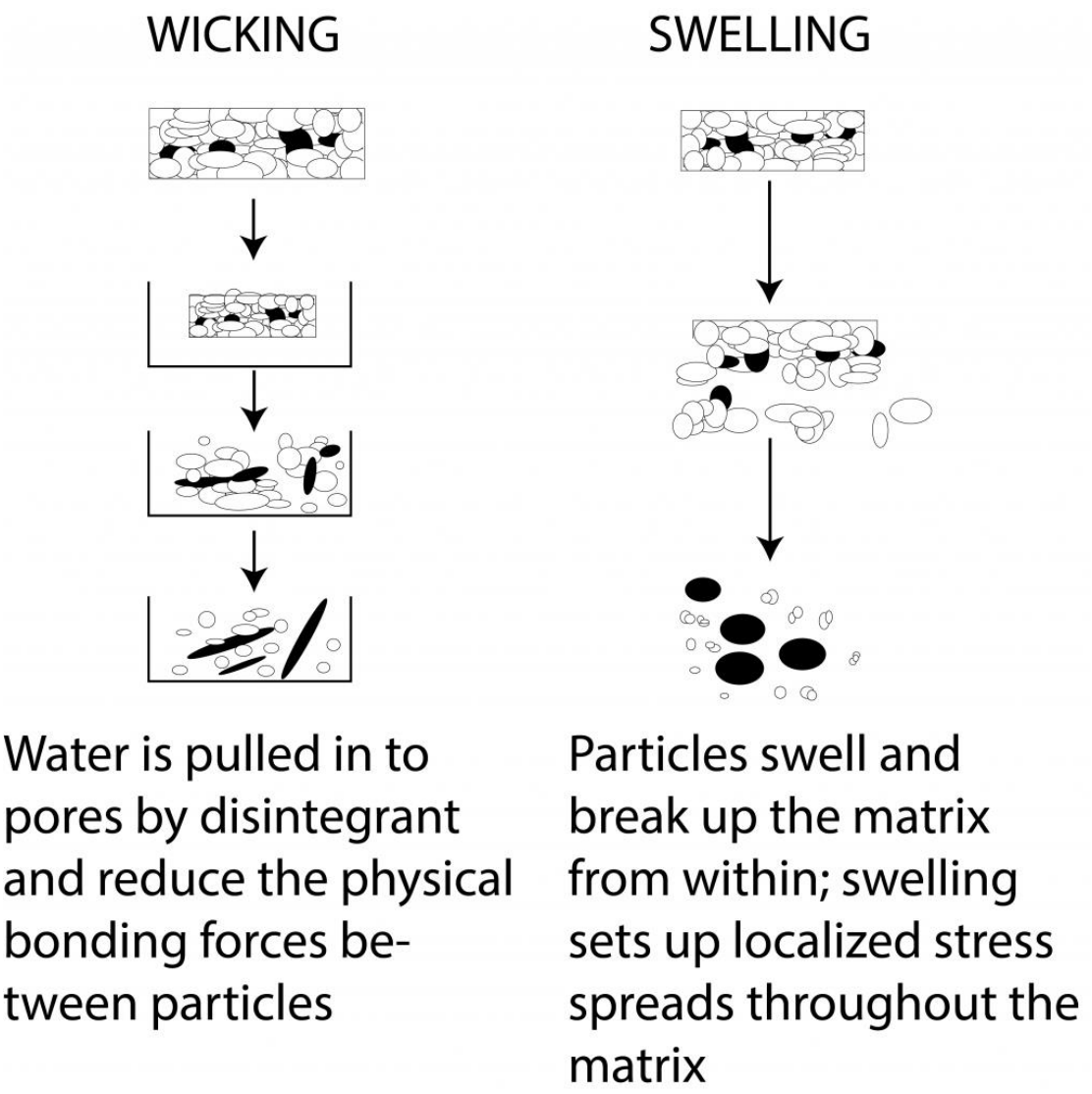


Granules with superdisintegrants in aqueous media Swelling of granules due to superdisintegrants

2. **Porosity and Capillary Action (Wicking):**

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart. E.g. Crospovidone, Crosscarmillose.[39]

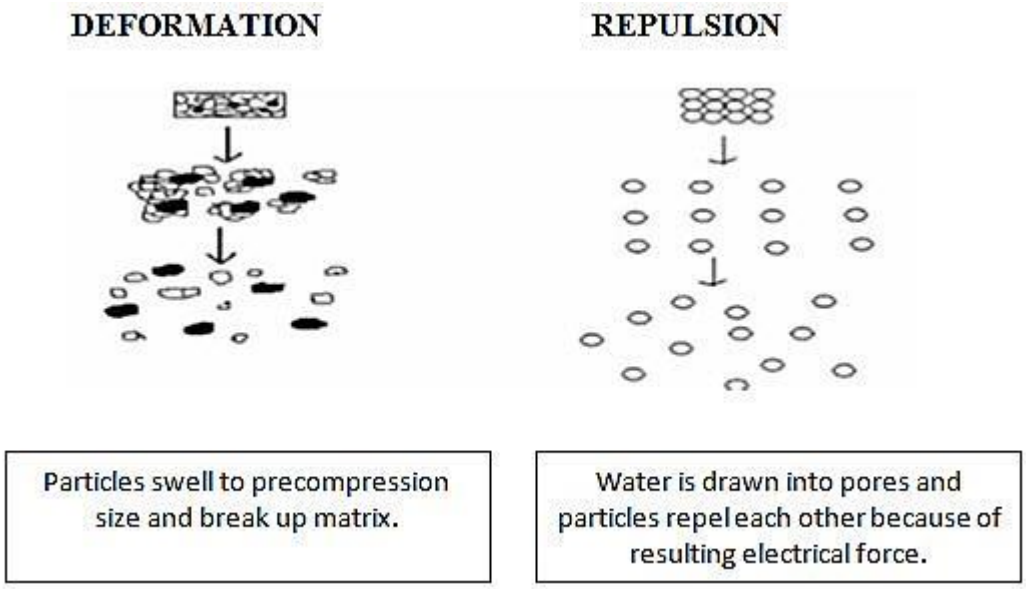
Fig.2. Wicking & Swelling



3. Deformation:

Starch grains are generally thought to be "elastic" in nature meaning that grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. In other words, the ability for starch to swell is higher in "energy rich" starch grains than it is for starch grains that have not been deformed under pressure.[40]

Fig.3. Deformation and repulsion



4. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with "nonswellable" disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

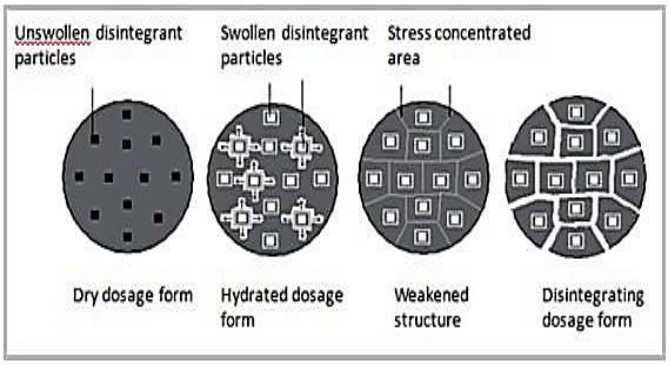
5. By Enzymatic Reaction:

Enzymes present in the body also act as disintegrants. These enzymes enhance the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.[41]

When it comes to immediate-release tablet formulations, the choice of disintegrant can have a significant effect on the

rate and extent of drug dissolution. Once a tablet disintegrates, the characteristics of the API, either alone or assisted by other formulation ingredients, determine the dissolution rate and extent of the API. Thus, the choice of superdisintegrant is important, especially with poorly soluble APIs.

Fig.4. Enzymes enhance helps in disintegration



1.14.NOT ALL SUPERDISINTEGRANTS ARE THE SAME:

The three most common classes of superdisintegrants are: crospovidone, croscarmellose sodium and sodium starch glycolate. In general, all of these provide rapid disintegration at low use levels in both wet and dry granulations and direct compression tablet processes; however, the classes of disintegrants differ in chemistry and particle morphology. Crospovidone possesses unique pyrrolidone chemistry and a highly porous particle morphology that results in high surface area. The high surface area combined with unique chemistry results in high-interfacial activity that serves to enhance the dissolution of poorly soluble drugs in a way that is not possible with other disintegrant technologies. Indeed, studies have shown that tablets containing a poorly soluble API and crospovidone, Type B, have significantly faster dissolution rates compared with tablets formulated with other superdisintegrants.

It has been widely reported that more than 60% of drugs in development and over 40% of recently launched drugs have issues related to poor solubility, leading to long development times or cancellations. Before evaluating advanced techniques, such as

amorphous solid dispersions, more traditional approaches such as the influence of superdisintegrants on dissolution are now being considered. The selection of a superdisintegrant and the use level plays a key role in determining the drug release of finished formulations.

1.15.CHOOSING AN OPTIMAL SUPERDISINTEGRANT:

It is important to consider the impact of the superdisintegrant with respect to the performance of the final dosage form. As drug dissolution is essential for absorption by the body, formulators no longer select disintegrants based on the lowest disintegration time because it is important to also consider the effect of the superdsintegrant on dissolution. Additionally, the ionic nature of both the API and the superdisintegrants must also be considered. Anionic superdisintegrants, such as croscarmellose sodium and sodium starch glycolate, can interact with cationic APIs and retard dissolution. Thus, nonionic superdistegrants are preferred when working with cationic APIs. Formulators also consider the impact of the superdisintegrant on physical tablet characteristics, such as tablet breaking force and friability. In today's high-speed tablet presses, superdisintegrants that provide tablets with high breaking force and low friability, while maintaining fast disintegration, are particularly important.[42]

1.16.SELECTION OF SUPERDISINTEGRANT:

Since superdisintegrant is used as an excipient in the tablet formulation, it has to meet certain criteria other than its swelling properties. The requirement placed on the tablet disintegrant should be clearly defined. The ideal disintegrants should have [43]

1. Poor solubility
2. Poor gel formation
3. Good hydration capacity
4. Good moulding and flow properties
5. No tendency to form complexes with the drugs

6. Good mouth feel.
7. It should also be compatible with the other excipients and have desirable tableting properties.

Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects. Different commonly used superdisintagrants are:[44]

1. **Modified Starches** - Sodium Carboxymethyl Starch (Chemically treated Potato Starch) i.e. Sodium Starch Glycolate (Explotab, Primogel).

   Mechanism of Action: Rapid and extensive swelling with minimal gelling.

   Effective Concentration: 4-6%. Above 8%, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects.
2. **Cross-linked polyvinylpyrrolidone** - water insoluble and strongly hydrophilic. i.e. crospovidone (Polyplasdone XL, Kollidon CL).

   Mechanism of Action: Water wicking, swelling and possibly some deformation recovery.

   Effective Concentration: 2-4%
3. **Modified Cellulose** - Internally cross-linked form of Sodium carboxymethyl cellulose. i.e. Ac-Di-Sol (Accelerates Dissolution), Nymcel

   Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling.

   Effective Concentrations: 1-3% (Direct Compression), 2-4% (Wet Granulation)

1.17.METHOD OF ADDITION OF SUPERDISINTEGRANTS:

There are three methods of incorporating disintegrating agents into the tablet.

i) Internal Addition

In wet granulation method, the disintegrant is added to other excipients before wetting the powder with the granulating fluid. Thereby, the disintegrant is incorporated within the granules. In dry granulation method, the disintegrant is added to other excipients before compressing the powder between the rollers. In a computer optimized experiment, the study show the effect of incorporating a disintegrant, croscarmellose sodium, intragranularly, extra granularly or distributed equally between the two phases of a tablet in which a poorly soluble drug constituted at least 92.5% of the formulation. The results analyzed by means of a general quadratic response surface model suggest that, tablets with the same total concentration of crosscarmellose sodium dissolve at a faster rate when the super disintegrant is included intragranularly. Tablet friability is not affected by the method of disintegrant incorporation.

ii)External Addition

In both wet and dry granulation method, the superdisintegrant is added to the granules during dry mixing prior to compression. The effect of mode of incorporation of superdisintegrants (croscarmellose sodium, sodium starch glycolate and crospovidone) on dissolution of three model drugs with varying aqueous solubility (carbamazepine, acetaminophen and cetrizine HCl) from their respective tablet formulations by wet granulation was studied. It is proved that crospovidone is effective in improving the dissolution of the drugs in extra granular mode of addition seems to be the best mode of incorporation, irrespective of the solubility of the main tablet component.

iii) Internal and External Addition

In this method, disintegrant is divided into two portions. One portion is added before granule formation (intra) and remaining portion is added to granules (extra) with mixing prior to

compression. This method can be more effective. If both intragranular and extragranular methods are used, extra- granular portion break the tablet into granules and the granules further disintegrate by intra-granular portion to release the drug substance into solution. However, the portion of intra-granular disintegrant (in wet granulation processes) is usually not as effective as that of extra-granular due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the intragranular disintegrant tends to retain good disintegration activity.[44]

Table-1 List of Common Disintegrants and Superdisintegrants

Name of excipients	Category	Concentration	Stability criteria
Alginic acid	Disintegrants	1-5%	Hydrolyzes slowly at room temperature
ColloidalSilicon Dioxide	Disintegrants	5-10%	Hydroscopic , but do not liquefy upon absorption of water
Cross- povidone	Superdisintegrants	2-5 %	As hygroscopic in nature, stored in an air- tight container, in a cool and dry place.
Methyl cellulose	Disintegrants	2-10%	Slightly hygroscopic, but stable
Micro-crystalline cellulose	Superdisintegrants	5-15%	Stable at dry and air tight condition
Starch	Superdisintegrants	5-10%	Stable at dry and air

1.18.ADVANTAGES OF SUPERDISINTEGRANTS:

The uses of superdisintegrants are extended in the applications of immediate release tablets, oral disintegration tablets, fast-dispersible tablets, capsules, mouth-dissolving films, etc

- Remarkable tendency on wetting causing rapid disintegration

- No lump formation on disintegration
- Compatible with commonly used therapeutical agents and excipients
- Work equally effective in hydrophilic and hydrophobic formulations.
- Provides good mechanical strength to the tablet facilitating easy packing and transportation.
- Does not stick to the punches and dyes.

- Although there are many superdisintegrants, which show superior disintegration, the search for newer disintegrants is ongoing and researchers are experimenting with modified natural products.[45]

1.19.EVALUATION OF TABLETS:

These tests are as following:-

1. Appearance
2. Thickness
3. Hardness
4. Weight variation
5. Friability
6. Disintegration
7. Uniformity of dispersion
8. Wetting Time
9. Water absorption ratio
10. Drug content
11. In vitro Dissolution
12. Stability studies

1.20.CHALLENGES AND LIMITATIONS FOR ODTS:

Drugs with relatively larger doses, are difficult to formulate into ODTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.

The application for technologies used for ODTs is limited by the amount of drug into each unit dose. The drug dose must be lower than 400mg for insoluble drugs and 60mg for soluble drugs.

However Flashdose technology can accommodate larger drug doses and offers improved mechanical strength. Orasolv® technology can accommodate a wide range of active pharmaceutical ingredient from 1 mg to 500 mg.

Mechanical strength - ODTs are made of porous or soft molded matrices in order to allow its disintegration in mouth. This makes tablet friable and handling becomes difficult.

Orodispersible tablets with highly porous structure and good mechanical strength have been developed by sublimation method. Also Durasolv® has much higher mechanical strength than Orasolv due to the use of higher compaction pressures during compression.

Palatability - ODTs are intended to be dissolved in mouth. Most of the drugs have bitter taste. Bitter taste can be masked with enough sweetener and flavors. Specifically, methods of taste masking include lipophilic vehicles, coating with polymers, carbohydrates, lipids or proteins complexation with cyclodextrins or ion-exchange resins, formation of salts, use of salting out layers and solid dispersions. OraQuick utilizes its own patented taste masking technology i.e. MicroMask®. In MicroMask® technology, taste-masking process is done by incorporating drug into matrix microsphere.

Drugs in form of ODTs are hygroscopic in nature and hence need to be protected from humidity. To overcome humidity problem special working facilities can be designed by simple methods and special air-conditioning systems can be set up. Size of tablet 7 and 8 mm are easy to swallow while tablets of size 8mm are easy to handle. Hence,

tablet sizes which are both easy to handle and swallow are difficult to achieve. For the patient compliance, to make the swallowing easier, round shape punches having optimum dimensions can be used.

Drug candidates should be stable both in water and in saliva, should not ionize at oral cavity pH and should be able to permeate oral mucosal tissue to diffuse and partition in upper GI epithelium (logP > 1, or preferably > 2, not have short half-life). To optimize solubility problem of the active pharmaceutical ingredient some solid buffers and surfactants can also be chosen.

ODT requires special packaging for proper stabilization and safety of stable product.

1.21.Future of ODTs:

ODT technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. "supergenerics" for veterinary or human application.

Some new quality control methods can be developed to determine the technological aspects of orally disintegrating tablets to define the characteristics of ODTs.

Protein and peptide–based therapeutics that used via oral route, have limited bioavailability when administered by immediate release tablets. Those kinds of products usually degrade immediately in gastrointestinal system. The developments of improved oral protein delivery Technology by ODTs, that dispersed and/or dissolved in the saliva, are very promising for the delivery of high molecular weight protein and peptide.

It would be an innovative improvement in the ODT technology when development of ODTs with controlled release properties that can deliver drugs which has short half-lives like 12–24 hours. The added convenience and compliance of such formulations will be used more immensely.

2. LITERATURE REVIEW

Nivedithaa V.R. *et al.*, [2018] has studied on the obesity is known to have significant impact on physical and psychological health related issues in many countries. Combination therapy of Atorvastatin Calcium, a lipid lowering agent and Bisoprolol Fumarate, an antihypertensive agent was preferred for obesity treatment. The present research work was envisaged to develop immediate release tablet of Atorvastatin Calcium and Bisoprolol Fumarate by direct compression method to minimize dose dependent side effect and improve patient compliance for obese people. The formulation that showed more than 90% release was considered to be optimized formulation of combination tablet. Study reveals that combination of beta-blocker and statins were good candidate for blood pressure and lowering lipoproteins in obese patient and may increases patient compliance by reducing the multi dosage form therapy and prescription costs.[34]

Safila Naveed *et al.*, [2016] has discussed about the stability of the pharmaceutical formulation during its entire shelf life in its final packaging as an important matter. Stability study does not only cover the physiochemical aspects of the drug but also explains the safety and efficacy of the product during its entire shelf life. Force degradation studies are the studies in which stress conditions or accelerated conditions are provided to the drug in bulk or product. For the development of stability indicating methods especially when insufficient information is accessible about degradation products and to obtain information about the degradation pathways and degradations products that might affect during storage conditions forced degradation studies are performed. Forced degradation studies help to facilitate pharmaceutical development, manufacturing, production and packaging where knowledge of chemical behavior can be used to improve drug

product. An FDA and ICH regulatory body portrays the layout of these stability limitations for the stability and degradation point of view.

Priyanka Patel *et al.*, [2015] has discussed that the Studies of drug-excipient compatibility represent an important phase in the preformulation stage for the development of all dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical, physical, therapeutical properties and stability of the dosage form. The present review contains a basic mode of drug degradation, mechanism of drug- excipient interaction like physical, chemical and biopharmaceutical. Different Thermal and Non-thermal method of analysis, Tools and software for incompatibility is also discussed. Once the type of interaction is determined we can take further steps to improve the stability of drug and dosage form. From review, we conclude that consequent use of thermal and non-thermal method provide data for drug- excipient interaction which can further help in selection of excipient for the development of stable dosage form.

Ramdooss Karthikeyan *et al.*, (2015) described the method of analysis for ambrisentan in pharmaceutical dosage form by reverse phase HPLC using C-18 coloumn(4.6 X 250mm) and 10mM phosphate buffer(pH 6.0), acetonitrile(50:50, v/v) is used as mobile phase and eluents were monitored at 226nm. The method has shown a good linearity in concentration range 6-30 mg/ml.

Honey Kanasara *et al.*, (2015) described the novel technique that can enhance the solubility of BCS class II drug. The technique includes use of cosolvents, Hydrotropy, Micronization, change in dielectric constant of solvent, amorphous forms, chemical modification of drug, use of surfactants, inclusion complex, alteration of pH of solvent, use of hydrates or solvates, use of soluble prodrugs, application of ultrasonic waves, functional polymer technology, controlled precipitation

technology, evaporative precipitation in aqueous solution, use of precipitation inhibitors, solvent deposition, precipitation, selective adsorption on insoluble carriers. Novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are size reduction technologies, lipid based delivery system, micellar technologies, porous micro particle technology. Solid Dispersion Technique and various types of solid dispersion systems have also been explained briefly.

Jishan Ali Ahmed *et al.*, (2015) expressed various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance. Sometimes immediate onset of action is considered obligatory immediate release tablets are the final option. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer and lead to better patient compliance. In the present work, we engage in discussion about formulation, development and evaluation of immediate release tablets. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

Virender Kaur *et al.*, (2015) studied about the disntegrants in Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution. The basic approach used in development tablets is the use of superdisintegrants like Cross linked Polyvinylpyrrolidone or crospovidone (Polyplasdone), Sodium starch glycolate (Primogel, Explotab), carboxymethylcellulose (Croscarmellose) etc. These superdisintegrants provide instantaneous disintegration of tablet after administration in stomach.[35]

Bhandari Neeraj *et al.*, [2014] has discussed that tablet is the most popular among all dosage forms existing today because of its convenience of self administration,compactness and easy manufacturing;

however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after adminstration. The basic approach used in development tablets is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmellose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration. The development of immediate release tablets also provides an opportunity for a line extension in the market place. A wide range of drugs (e.g., cardiovascular drugs, analgesics, antihistamines, and drugs can be considered candidates for this dosage form. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. Immediate release dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. Now a day, immediate release formulations are similar to many sustained release formulations that are now commonly available.[9]

Shweta Gupta *et al.*, [2013] has discussed that Poorly water-soluble drug candidates are becoming more prevalent. It has been estimated that approximately 60–70% of the drug molecules are insufficiently soluble in aqueous media and/or have very low permeability to allow for their adequate and reproducible absorption from the gastrointestinal tract (GIT) following oral administration. Formulation scientists have to adopt various strategies to enhance their absorption. Lipidic formulations are found to be a promising approach to combat the challenges. In this review article, potential advantages and drawbacks of various conventional techniques and the newer approaches specifically the self-emulsifying systems are discussed. Various components of the self-

emulsifying systems and their selection criteria are critically reviewed. The attempts of various scientists to transform the liquid self-emulsifying drug delivery systems (SEDDS) to solid-SEDDS by adsorption, spray drying, lyophilization, melt granulation, extrusion, and so forth to formulate various dosage forms like self emulsifying capsules, tablets, controlled release pellets, beads, microspheres, nanoparticles, suppositories, implants, and so forth have also been included. Formulation of SEDDS is a potential strategy to deliver new drug molecules with enhanced bioavailability mostly exhibiting poor aqueous solubility. The self-emulsifying system offers various advantages over other drug delivery systems having potential to solve various problems associated with drugs of all the classes of biopharmaceutical classification system(BCS).[8]

Pranay Wal *et al.*, [2013] has described that Increasing numbers of experimental investigations and recently also of clinical trials strongly suggest an integral involvement of the endothelin (ET) system in the pathophysiology of a variety of disease states, mainly of the cardiovascular system. Ambrisentan (LU208075)approved by the US Food and Drug Administration in 2007, a selective ETA-receptor antagonist, is an orally active diphenylpropionic acid derivative that was recently approved for treatment of pulmonary arterial hypertension (PAH) in patients with World Health Organization class II or III symptoms.. It has been shown to have a very promising efficacy to safety ratio in the initial clinical trials. Phase II and Phase III trials with ambrisentan in pulmonary arterial hypertension have been performed. Pulmonary arterial hypertension (PAH) is a rare and progressive disease of the pulmonary arterial circulation that is characterized by a progressive rise in pulmonary vascular resistance, eventually leading to right-heart failure and death. Endothelin (ET) is a potent vasoconstrictor with mitogenic, hypertrophic and pro-inflammatory properties. Therefore,

blockade of ET receptors has been suggested as an attractive target in a number of acute and chronic cardiovascular indications, including pulmonary arterial hypertension (PAH), systemic hypertension, and heart failure. In Phase III clinical trials in patients with PAH, ambrisentan (2.5–10mg orally once-daily) improved exercise capacity, time to clinical worsening, WHO functional class, and quality of life compared with placebo. This review discusses the endothelin family of proteins and receptors and their role in the pathophysiology of pulmonary hypertensive diseases.

Sarfaraz *et al.*, (2013) Immediate release tablets are highly accepted fast growing drug delivery systems and thus, an attempt was made to improve the onset of action of drug. To achieve this goal, selective superdisintegrants croscarmellose sodium, crospovidone and sodium starch glycolate in different concentrations (2.5 – 7.5%w/w), were evaluated for their effect on the disintegration behaviour of tablets, while microcrystalline cellulose and lactose were used as diluents. The tablets were prepared by direct compression method and were evaluated for various physicochemical properties, FTIR, in vitro disintegration and in vitro drug release studies.[12]

Rajesh *et al.*, (2012) The task of developing immediate release tablet is accomplished by using suitable diluents and superdisintegrants. Faster disintegration of the tablet administrated orally minimizes absorption time and improves its bioavailability in less time. The formulation development work was initiated with wet granulation method and a total of 8 formulations (F1-F8) were made. The formulated tablets were evaluated for various pre compression parameters and post compression parameters like thickness, hardness, weight variation, friability, disintegration test, drug content uniformity and in vitro release studies. The formulation F8 showed satisfactory physical parameters, and it was found to be stable among other formulations.

Natarajan R *et al.*, (2011) to formulate various formulations of immediate release tablet of Paroxetine using different superdisintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone) and different grades of di calcium phosphate by wet granulation method. The drug-excipients interaction was investigated by FTIR. The granules and tablets of Paroxetine were evaluated for various pre and post compression parameters like Angle of repose, Compressibility index, Hausner's ratio, Tablet hardness, Friability, Weight variation, Drug content and in vitro dissolution. Their results were found satisfactory. The in vitro dissolution studies show the release is in the following order of superdisintegrants: Sodium Starch Glycolate>Croscarmellose>Crospovidone. These results suggest that, as determined by f2 factor (similarity factor) and maximum in vitro dissolution was found to be with Formulation F-7 and it clearly shows due to Sodium Starch Glycolate (4%).[10]

Patel N. *et al.*, (2011) Opadry White was used for coating the core tablets. Total 16 batches were formulated. In that last 6 batches were optimized by process parameters like kneading time, lubrication time and by sizing. These formulations were evaluated for physical parameters of tablet, drug-excipient compatibility study, and in- vitro drug release study. The optimize formulation F8 release profile was match with marketed formulation and release rate was maximum than other batches. Stability study of the optimized formulation indicates no significant differences in release profile and drug content after a period of one to three month. Immediate release dosage form of API was formulated using Cros carmellose Sodium as superdisintegrant. [11]

Sheen *et al.*, (1995) studied the formulation of poorly water-soluble drug in solid dispersion to improve bioavailability. The results concluded that the bioavailability of poorly water-soluble drug was increased from water-soluble carrier and was further improved by the addition of a surfactant.

3.1. AIM

The main aim of the work is to formulate immediate release tablets of Ambrisentan 10 mg by a direct compression method and to evaluate the prepared tablets against the marketed product, Letairis®.(Ambrisentan tablets, 10 mg)

3.2. OBJECTIVE

Challenges

- To develop a cost effective formulation with direct compression method with commercialization aspect.
- Direct compression process and with limited excipients will be cost effective.
- Low solubility of API.
- To develop a robust formulation free from defects in flow and compression.
- Since the drug load on the formulation is less than 10%, overcoming the challenge of blend uniformity and content uniformity with limited manufacturing steps is a challenge.
- Attaining uniform stability results of the finished product after being processed.

4. PLAN OF WORK

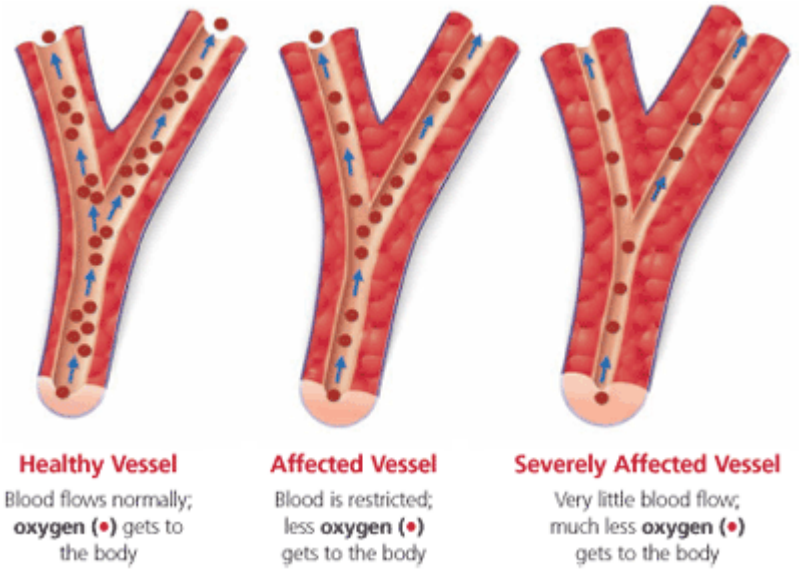
- Literature survey.
- Procurement of drug, other excipients.
- Preformulation Studies[3]
    - Solubility
    - Drug and excipient compatibility studies
    - Bulk density
    - True density
    - Melting point determination
    - Carr's index
    - Hausner's ratio
    - Angle of repose
- Formulation development
- Evaluation Studies[3]
    - Weight variation
    - Hardness
    - Friability
    - Thickness
    - Disintegration time
    - Content uniformity
    - *Invitro* Dissolution study
    - Stability Studies

5. DISEASE PROFILE- PULMONARY ATREIAL HYPERTENSION

5.1. INTRODUCTION:

Pulmonary aterial hypertension is a syndrome resulting from decreased flow of blood in the pulmonary vascualte due to increased pulmonary vascular resistance (PVR) and right heart failure[13]. The Revised world health organization (WHO) Classification has divided pulmonary hypertension into five types. The incidence of PAH is 15/million in the population.

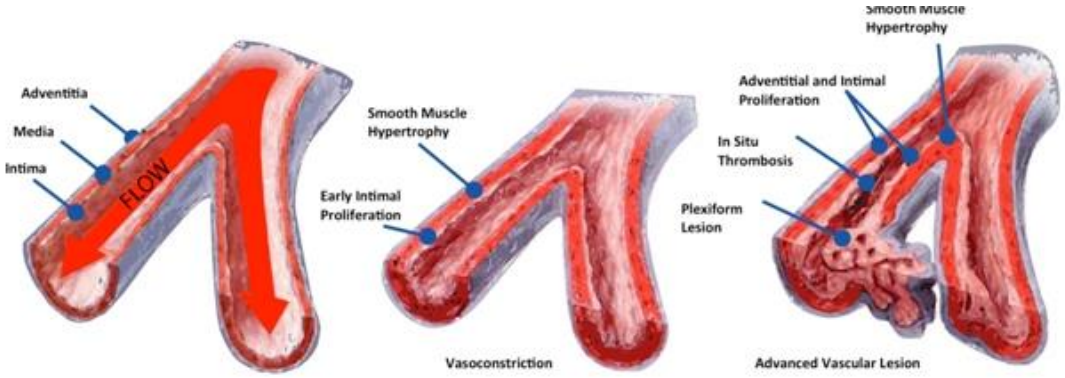
Fig.No:5. Difference between Healthy and affected vessel



Pulmonary arterial hypertension is associated with increased PVR resulting from loss of vascular luminal cross-section due to vascular remodeling produced by excessive vasoconstriction plays a significant role in approximately 20% of patients[14]. Pulmonary arterial hypertension is a panvasculopathy predominantly affecting small pulmonary arteries[15]. Pulmonary arterial hypertension is characterized by a variety of arterial abnormalities including intimal hyperplasia, medialhypertropy, adventitial proliferation and thrombosis in situ. Right ventricle function is a major determinant of functional capacity and prognosis in PAH(1) while RV hypertrophy and dilation is initiated by increased after load, the adequacy of RVs compensatory response is quite variable amongst individuals. Plumonary arterial hypertension is characterized by endothelial

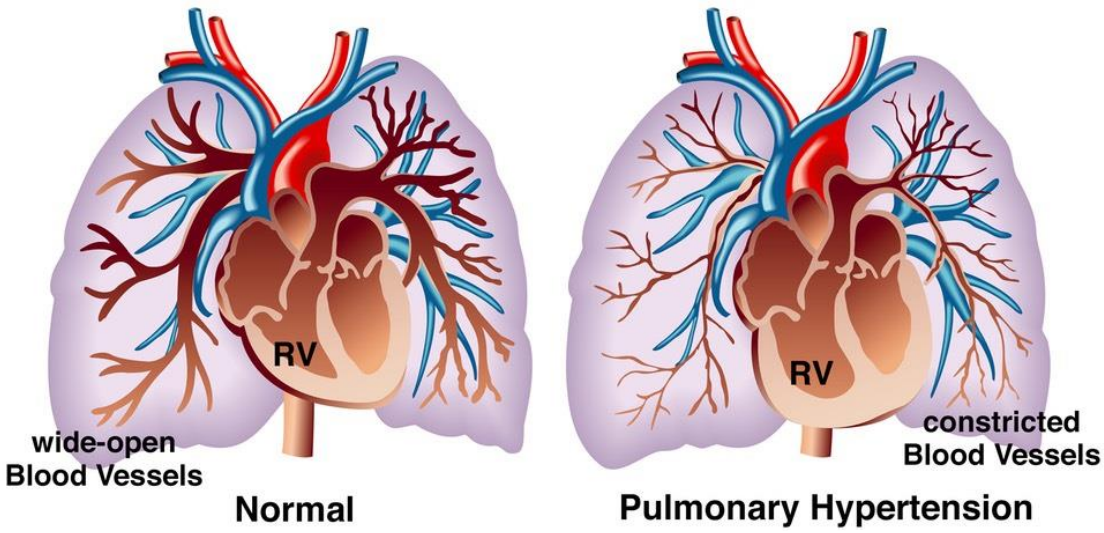
dysfunction, a decreased ratio of apoptosis/proliferation in pulmonary artery smooth muscle cell and thickened disordered adventitia in which there is excessive activation of adventitial metalloprotease[16].

Fig.No:6. Pulmonary vascular changes in PAH leading to RV strain



PAH is characterized by platelets that are depleted by serotonin and elevation of plasma serotonin. In PAH, endothelial dysfunction is characterized by increased production of vasoconstrictor/mitogenic compounds such as endothelin and thromboxane and deficient production of vasodilators like prostacycline, there is also increased production of thromboxane A2 and deficient prostacyclin[17] leading to thrombosis, proliferation and vasoconstriction.

Fig.No:7. Difference between normal and affected vessel in lungs



Decreased level of endothelial nitric oxide has been observed in PAH as it is quickly inactivated by PDE-5. Endothelian-1 is a

vasoconstrictor and a smooth muscle mithogen that may contribute to the development of PAH.

5.2.CLASSIFICATION OF PAH AS PER WHO:

- Pulmonary arterial hypertension
    - Idiopathic PAH
    - Familial PAH
    - Associated with PAH
- Connective tissue disorder
- Congential systemicto pulmonary shunts
- Portal hypertension
- Human immunodeficiency virus infection
- Drugs and toxins
- Pulmonary hypertension with left heart disease
- Pulmonary hypertension associated with lung disease or hypoxemia
- Pulmonary hypertension due to chronic thrombolic or embolic disease

5.3.CAUSES :

- History of heart murmur
- Deep venous thrombosis (DVT) or pulmonary embolism (PE)
- Raynaud phenomenon
- Arthritis or arthralgias
- Rash
- Heavy alcohol consumption
- Hepatitis
- Heavy snoring
- Daytime hypersomnolence
- Morning headaches
- Morbid obesity
- Family history of pulmonary hypertension
- Drug use, in particularly diet drugs and illicit drugs
- Medications

5.4. SYMPTOMS:

Patients with PAH may also have nonspecific symptoms secondary to pulmonary hypertension. These may include the following:

- Dyspnea upon exertion
- Fatigue
- Lethargy Dizziness or fainting spells (syncope)
- Syncope with exertion
- Chest pain
- Anorexia
- Right upper quadrant pain
- welling (edema) in your ankles, legs and eventually in your abdomen (ascites)
- Bluish color to your lips and skin (cyanosis)
- Racing pulse or heart palpitations

Less common symptoms include the following:

- Cough
- Hemoptysis
- Hoarseness (due to compression of the recurrent laryngeal nerve by the distended pulmonary artery)

5.5. PAH Diagnosis:

1. **Blood tests**: potential diseases that are associated with PAH as well as other signals of PAH. These include an HIV test; thyroid tests; autoimmune disease panels to test for systemic lupus erythematosus and scleroderma; liver tests; as well as standard tests like a complete blood count (CBC) and chemistry tests. It may also include a test to measure a hormone called brain natriuretic peptide (BNP) that helps evaluate the amount of stress on the heart.
2. **Chest X-ray**: A chest X-ray gives a picture of heart, lung, and chest to look for signs of pulmonary hypertension.
3. **CT scan**: A CT scan provides with a more detailed, visual picture of lungs, blood vessels and heart.

4. **Electrocardiogram**: This noninvasive test shows the electrical activity of the heart and can detect abnormal heart rhythms. It is a useful test to identify different causes for symptoms associated with PAH.
5. **Pulmonary function tests**: These simple breathing tests measure how much air you can hold in your lungs and how much air moves in and out of your lungs.
6. **Exercise tolerance test** (also known as the 6-minute walk test): This test is used to compare exercise capacity, oxygen levels and symptoms over time and to evaluate how these characteristics change over time and with therapy.
7. **Cardiopulmonary exercise testing** (CPET or CPX): This test measures how well heart and lungs are performing both at rest and during exercise. CPET helps to understand the amount of oxygen your body is using, the amount of carbon dioxide body is producing, and the breathing pattern.
8. **Ventilation-perfusion scan** (VQ scan): This test examines air and blood flow to the lungs and creates images use to look for blood clots in the lungs.
9. **Echocardiogram**: This noninvasive test – a type of ultrasound of the heart – looks at the chambers and valves of the heart, determining their size and function. An echocardiogram will detect some signs of PH in most patients with the disease, making it very practical. While it does not directly measure pulmonary arterial pressure (PAP), it does give an idea if PH is present and how severe it is. Unfortunately, it cannot guarantee the diagnosis of PH by itself, which means further testing is likely.
10. **Cardiac MRI** (Magnetic Resonance Imaging): This is an MRI test that evaluates the heart size and function more accurately than the echocardiogram and gives a better picture of the heart muscles, valves, and blood work. It may also show any

congenital heart disease (an abnormality in the heart that developed before birth).

11. **Right-sided heart catheterization**: will likely recommend a right-sided heart catheterization because it is the clearest test for showing which of the five forms of PH. This test involves placing a small tube, known as a catheter, into a large vein in the neck, arm, or groin. This catheter is then threaded through the different chambers of the heart and lung to measure the pressure in each. How much blood the heart pumps each minute, known as cardiac output, is also measured. The amount of resistance to blood flow in the lungs, known as the pulmonary vascular resistance, can be calculated from these measurements and are important indicators of how severe PAH is.

5.6. TREATMENT:

A) MEDICATION:

1. **Calcium Channel Blockers:** Nifedipine, Diltiazem, Amlodipine
2. **Vasodilators:** Epoprostenol, Treprostinil, Iloprost
3. **PAH, Prostacyclin Agonists:** Selexipag
4. **Endothelin-Receptor Antagonists :** Bosentan, **Ambrisentan,** Macitentan
5. **Phosphodiesterase-5 Enzyme Inhibitors :** Sildenafil, Tadalafil, Vardenafil
6. **Soluble Guanylate Cyclase (sGC) Stimulators:** Riociguat
7. **Cardiac Glycosides:** Digoxin
8. **Loop Diuretics :** Furosemide, Bumetanide
9. **Anticoagulants:** Warfarin
10. **Oxygen.**

B) SURGERY:

- **Atrial septostomy.** If medications don't control pulmonary hypertension, this open-heart surgery might be an option. In an atrial septostomy, a surgeon will create an opening between the

upper left and right chambers of heart (atria) to relieve the pressure on the right side of heart. Atrial septostomy can have serious complications, including heart rhythm abnormalities (arrhythmias).

- **Transplantation.** In some cases, a lung or heart-lung transplant might be an option, especially for younger people who have idiopathic pulmonary arterial hypertension.

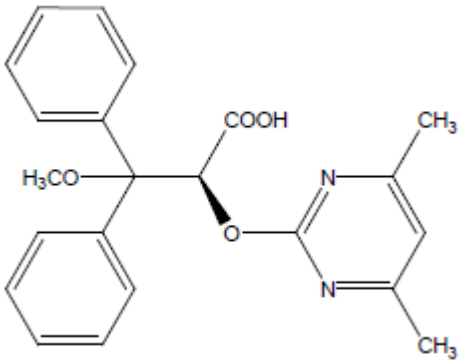
  Major risks of any type of transplantation include rejection of the transplanted organ and serious infection, and you must take immunosuppressant drugs for life to help reduce the chance of rejection.

6. DRUG PROFILE - AMBRISENTAN

Description:

Ambrisentan, is an orally active endothelin receptor antagonist that is selective for the endothelin type-A (ETA) receptor antagonist indicated for the treatment of pulmonary arterial hypertension. As an endothelin receptor antagonist, Ambrisentan prevents endogenous endothelin peptide from constricting the muscles in blood vessels, allowing them to relax and permit a reduction in blood pressure. It contains a single chiral center determined to be the (S) configuration. Ambrisentan was approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency, and designated an orphan drug, for the treatment of pulmonary hypertension.

Chemical Structure



CAS number

177036-94-1

IUPAC Name

(*S*)-4-({3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl}methyl)-1,3-oxazolidin-2-one

Description

White to off- white powder

Drug class

Pulmonary Arterial Hypertension Agents

BSC Classification Class II

Water Solubility

Ambrisentan is practically insoluble in aqueous solutions at low pH. Solubility increases at higher pH.

pKa 4

Molecular weight: 378.428 g/mol

Pharmacodynamics:

Ambrisentan is an orally active, non-sulfonamide, propanoic – class, endothelin receptor antagonist (ERA) that is selective for endothelin type A (ET_A) receptor. ET_A receptor antagonist inhibit phospholipase C-mediated vasoconstriction and protein kinase C-mediated cell proliferation, while preserving nitric oxide and prostacyclin production, cyclic GMP- and cyclic AMP –mediated vasodilation, and endothelin-1 (ET-1) clearance that is associated with the endothelin type B (ET_B) receptor. ERAs have proven therapeutic benefit in treatment of PAH in humans.Ambrisentan has a high affinity against myocardial native ET_A receptor, with selectivity for the ET_A receptor of approximately 4000-fold relative to the ET_B receptor.

It is indicated for treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension (PAH) associated with connective tissue disease in patients with WHO functional class II or III symptoms.

Pharmacokinetics:

Absorption:

Ambrisentan was well absorbed following oral administration. It also showed high absolute oral bioavailability, indicating that it undergoes little or no first pass metabolism. C_{max} occurring around 1.5 hours post dose under both fasted and fed condition. C_{max} and AUC increase dose proportionally over the therapeutic dose range.

Distribution:

Ambrisentan binds to plasma proteins to a higher extent (98.9%) and specifically albumin was the primary binding protein.

Metabolism:

Ambrisentan is metabolized by phase I oxidative metabolism and by phase II hepatic glucuronidation. About 30% of the administered dose undergo oxidative metabolism mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19. The identified metabolites of ambrisentan includes

- 4,6 dimethyl-2-hydroxypryimidine(M1)
- Ambrisentan glucuronide (M2)
- Hydroxylated ambrisentan (M3)
- O-demethylated ambrisentan (M4)
- Dihydroxylated ambrisentan (M5)
- Dihydroxylated ambrisentan glucuronide (M6)
- Hydroxylated ambrisentan glucuronide (M7)
- O-demethylhydroxymethyl ambrisentan (M8)

Excretion:

The major route of elimination of elimination for ambrisentan and its metabolites is biliary excretion in faeces (65.4%), with urinary excretion (22.1%) representing minor route.

Drug indication:

Ambrisentan is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Studies establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

DOSAGE AND ADMINISTRATION:

Adult Dosage

Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Ambrisentan 10 mg or tadalafil 40 mg.

SIDE EFFECTS:

Clinically significant adverse drug reactions that appear which includes,

- Embryo-fetal Toxicity
- Fluid Retention
- Pulmonary Edema with PVOD
- Decreased Sperm Count
- Hematologic Changes

Brand names

Letairis®(Ambrisentan tablets) 10 mg

Uses:

Ambrisentan is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

7. EXCIPIENT PROFILE

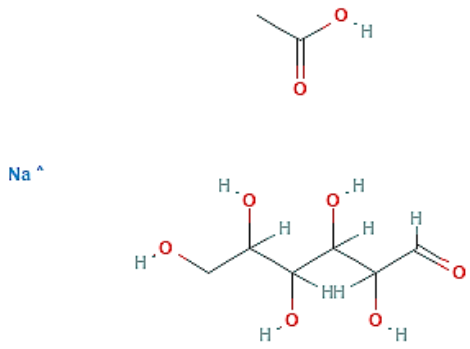
7.1 CROSCARMELLOSE SODIUM[20]

Synonym :

Ac-Di-Sol;Crosslinkedcarboxymethylcellulose sodium; Modified cellulose gum; Pharmacel XL; carmellosumnatricumconexum.

Description : White odorless or greyish white powder.

Structure :



IUPAC name: Acetic acid;2,3,4,5,6-pentahydroxyhexanal;sodium

Chemical name:

Croscarmllose; Sodium Carboxymethylcellulose; Carmellose

Molecular formula : $C_{28}H_{30}Na_8O_{27}$

Molecular Weight : 982.44 g/mol

Solubility:

Insoluble in water, although croscarmellos Sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Safety :

It is a nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may havea laxative effect, although the quantities usedin solid dosage formulations are unlikely to cause such problems.

Application

- Disintegrant for capsules, tablets, and granules
- Disintegrant in tablets : 0.5 – 5.0 %

- Disintegrant in capsules : 10 – 25 %

Stability and storage conditions:

- Croscarmellose sodium is a stable though hygroscopic material.
- Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

7.2. LACTOSE MONOHYDRATE[20]

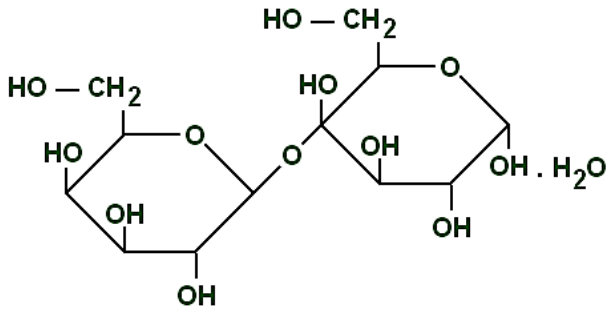
Synonym:

CapsuLac; GranuLac; Lactochem; lactosummonohydricum; Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac; SpheroLac; Super Tab 30GR; Tablettose.

Description:

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet

Structure :



IUPAC name:

(2R,3R,4S,5R,6S)-2-(hydroxymethyl)-6[(2R,3S,4R,5R)-4,5,6-trihydroxy-2-(hydroxymethyl)oxan-3yl] oxyoxane-3,4,5-triol

Chemical name:

O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate

Molecular formula : $C_{12}H_{22}O_{11}H2O$

Molecular Weight : 360.31

Solubility : Practically insoluble in chloroform, ethanol, ether.

Water

- 1 in 5.24
- 1 in 3.05 at 40^0C
- 1 in 2.30 at 50^0C
- 1 in 1.71 at 60^0C
- 1 in 0.96 at 80^0C

Melting point : 201–202^0C

Applications :

Lyophilization aid, Tablet binder, Tablet and capsule diluent, Tablet and capsule filler.

Storage :

Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions; Lactose should be stored in a well-closed container in a cool, dry place.

7.3. MICROCRYSTALLINE CELLULOSE[20]

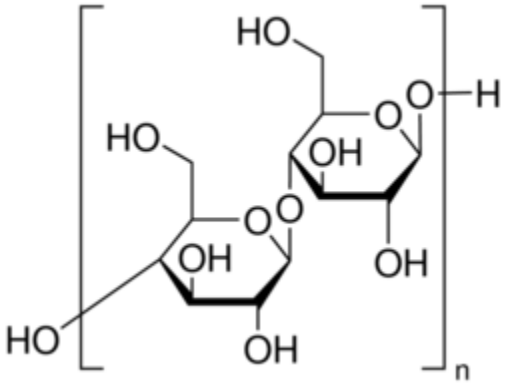
Synonym :

Avicel PH; Cellulose gel; Crystallinecellulos; E460; Emcocel; Fibrocel; Tabulose; Pharmacel.

Description :

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles

Structure :



IUPAC name:

2-[4,5-dihydroxy-2-(hydroxymethyl)-6-methoxyoxan-3-yl]oxy-6-(hydroxymethyl)-5-methoxyoxane-3,4-diol

Chemical name: Cellulose gel; Cellulose, microcrystalline

Molecular formula: $C_{14}H_{26}O_{11}$

Molecular Weight :370.351 g/mol

Solubility :

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents

Melting point : Chars at 260–2708C.

Applications :

Adsorbent, Suspending agent, Tablet and capsule diluent, Tablet disintegrant

Safety :

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Storage :

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

7.4. MAGNESIUM STEARATE[20]

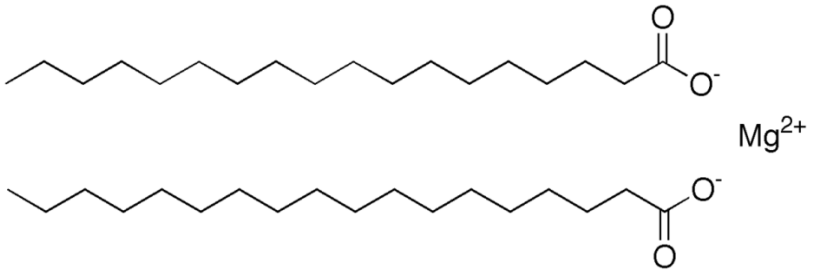
Synonym :

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesiumsalt; stearic acid, magnesium salt; Synpro 90.

Description :

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Structure :



IUPAC name : Magnesium; octadecanoate

Chemical name :

Magnesium stearate; Magnesium octadecanoate; Magnesium distearate; Synpro 90; Octadecanoic acid,

Molecular formula : $C_{36}H_{70}MgO_4$

Molecular Weight : 591.24 g/mol

Solubility :

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Melting point : 117–150^{0}C

Applications : Tablet and Capsule Lubricant

Safety :

It is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

Storage:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

8. MATERIALS AND EQUIPMENTS USED

8.1. Active pharmaceutical Ingredient

Table 2. Active Pharmaceutcal Ingredient and its manufacturer.

API	Manufacturer
Ambrisentan	Aurobindo Pharma

8.2. Excipients

Table 3. Excipients and its manufacturers.

Excipients	Manufacturer
Lactose Monohydrate	SPI Pharma
Microcrystalline cellulose PH101	Roquette Pharma
Croscarmellose sodium	Avantor Performance Materials
Magnesium Stearate	Firmenich Pharma

8.3.Equipments used:

- Analytical balance,
- Sieves,
- Proton mini press compression machine, 10 station,
- vernier calliper,
- Electrolab Friability tester,
- Hardness tester,
- Electrolab Tap Density Tester,
- Electrolab Disintegration Tester,
- Ohaus Moisture analyser,
- Funnel and stand for Angle of repose,
- UV spectrophotometry,
- Dissolution test apparatus,
- Water's HPLC

9. PREFORMULATION

It is the first step in rational development of dosage forms of drug substance. Preformulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms that can be mass-produced. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture and pharmacokinetic biopharmaceutical properties of the resulting product.

Preformulation parameters

9.1.Organoleptic properties

This includes recording of appearance,colour, odour and taste of the drug using descriptive terminology. Record of colour of early batches is very useful in establishing appropriate specifications for later production. Colour white.

9.2.Physicochemical characterization:

9.2.1.Density measurement:

Granules density may influence compressibility, tablet porosity, dissolution and other properties. Different types of density calculation were done to characterize the API and its flow property. Generally two types of density are determined i.e., bulk density and tapped density. The methods followed for calculation of the above two densities are determined by the following ways.

9.2.2.Bulk density:

It is a measure used to describe the packing of particles or granules. An accurately weighed quantity of powder, which was previously passed through sieve #40 [USP] and carefully poured bed was made uniform without disturbing. Then volume measure was called as the bulk volume and the bulk density is calculated by following formula.

Bulk density= weight of powder / Bulk volume

9.2.3.Tapped density:

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to300 taps drop per minute and operated for 500 taps. Volume was noted as (V_a)and again tapped for750 times and volume was noted as (V_b). If the difference between V_a and V_b not greater than 2% then V_b is considered as final tapped volume. The tapped density is calculated by the following formula.

Tapped density= Weight of powder /Tapped volume

9.2.4.Flow properties:

The flow properties from a material result from many forces. There are many types of forces hat can act between solid particles: frictional forces, surface tension forces, mechanical forces caused by interlocking of particles of irregular shapes, electrostatic forces and cohesive or van der vaals forces. These forces can effect granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy and surface area.

9.2.5.Compressibility index:

Pharmaceutical powders are broadly classified into free flowing and cohesive. Powders are more often compressed into tablets using a pressure of 5kg/cm^2. This is called compression or compaction. During this process the porosity of the powder changes. The compression properties of most drugs are very poor. Therefore compression vehicles such as lactose, calcium phosphate and microcrystalline cellulose are included in tablet formulations. Normally low dose drugs (<50mg) are prepared by direct compression. Tablet materials should be plastic that is capable of undergoing permanent deformation yet exhibit brittleness. Percentage compressibility also known as Carr's consolidation index is indirectly

related to the relative flow rate, cohesiveness and particle size. It is a simple, fast and popular method for predicting powder flow characteristics.

Table 4. compressibility and flowability.

Percentage compressibility	Flowability
5-10	Excellent
12-16	Good
18-21	Fair
23-25	Poor

Carr's consolidation index= [(Tapped density-Fluff density)/tapped density]*100

Compressibility index can be a measure of the potential strength that a powder could build up in its arch in a hopper and also the ease with which such an arch should be broken.

9.2.6.Angle of repose

The angle of Repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\theta = \text{Tan}^{-1} (h/r)$$

Where

'h' = height of the pile

'r' = radius of the pile

Values of θ are rarely less than 20^0, and values of up to 40^0 indicate reasonably flow potential. Above 50^0, however, the powder flows only with great difficulty. In general, the angle of repose increased with decreasing particle size. The addition of talk in low concentration decreases the repose angle, but in higher concentration it increases the angle.

Table 5. Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degree)
Excellent	25-30
Good	31-35
Fair – aid not needed	36-40
Passable - may hang up	41-45
Poor – must agitate, vibrate	46-55
Very poor	56-65
Very very poor	>66

9.2.7.Hausner ratio

It is the ratio of bulk volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. Thiscan be calculated by the formula

Hausner 's ratio=Tapped density/Bulk density

Value < 1.25 indicate good flow (=20% carr's index)

While > 1.50 indicate poor flow (-35% carr's index)

Table 6. Flow property and corresponding Hausner's ratio.

Flow Character	Hausner's Ratio
Excellent	1.2-1.3
Good	1.3-1.4
Fair	1.4-1.5
Poor	1.5-1.6

9.2.8.Particle size distribution

Particle size distribution is a very important in process technique of final blend after blending. It is an important parameter to determine the amount of fines as well as particle with larger particle size in final blend. It also helps in keeping a check over uniformity of distribution of blend over various sizes while carrying out consecutive batches. Particle size determination was carried by arranging various sieves of sizes #20, #40, #60, #80, #100, #140, #200 and Pan (for finer

particles which passes even #200 sieve) in ascending order (i.e.,#20 sieve lies on top and pan at the bottom). Then the final blend of accurately weighed quantity was placed on the top sieve. And the sieves are placed in vibrosifter and allowed to run at 1.0 amplitude for 10 minutes. After the procedure difference of initial and final weight of sieves were noted to calculate the percentage retention of the blend in various sieves.

10. FORMULATION

Batches and their composition:

Various batches were planned and executed with the unit concentration of the ingredients used in the batch as shown in the table below.

Table 7. Composition of unit dose of various trial batches.

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Ambrisentan	10	10	10	10	10	10	10
2	Lactose Monohydrate	98	91	84	77	70	63	56
3	Microcrystalline cellulose pH 101(MCC)	14	21	28	35	42	49	56
4	Croscarmellose sodium (CCS)	15	15	15	15	15	15	15
5	Magnesium stearate	3	3	3	3	3	3	3
	Total	**140**	**140**	**140**	**140**	**140**	**140**	**140**

Procedure:

1. Weigh the API and excipients as per the above formula.
2. Sift the item #01, 02, 03 in #30 mesh.
3. Blend all the ingredients.
4. After blending the above mixture is prelubricated with magnesium stearate.
5. Collect pooled sample blend for characterization.
6. Compress the final blend in a protn mini press rotary tablet press with a target weight of 140 mg.
7. Collect the tablets, pick the tablets randomly and evaluated.

11. EVALUATION.

11.1.Physical appearance

The physical appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Included in this category are tablet sizes, shape, colour, presence or absence of any odour, taste, surface texture, physical flaws and consistency and legibility of any identification marking.

11.2.Weight variation

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. Each tablet weight was then compared with average weight variation. Each tablet weight was then compared with average weight to ascertain the weight of the tablets within the permissible limits. Not more than two of the individual weights should deviate from the permissible limits. Not more than two of the individual weights should deviate from the average weight by more than 5% for >300mg tablets and none by more than double that percentage.

Percentage deviation= [(Tablet weight- Average weight)/tablet weight]*100

Table.8 USP Specification for uniformity of weight.

S.No	Weight (mg)	Maximum percentage difference allowed
1.	130 or Less	10
2.	130 - 324	7.5
3.	More than 324	5

11.3.Loss on drying

Loss on drying is an important parameter to determine the moisture intake by blend during processing. Limit on loss on drying is established from the sum of percentage moisture intake values of each excipients used in the process. Percentage moisture in take was determined during in process by using Ohaus Moisture Analyser. In

which 1gm of blend was placed after taring the instrument at 105°C in auto mode.

11.4.Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\textbf{Percentage friability}=[(w_2-w_1)/w_1]*100$$

Where, W_1= Weight of tablets before test; W_2= Weight of tablets after test

11.5.Thickness

The thickness was measured by using vernier calliper and values were tabulated. Ten tablets of each batch were measured. Average and standard deviation was calculated.

11.6.Hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Erweka hardness tester.

11.7.Disintegration test

Breaking of tablets into smaller particles or granules is known as disintegration and time taken for breaking of tablets in a suitable medium is called disintegration time (DT). This test is not applicable to modified-release tablets and tablets for use in the mouth. For those tablets for which the dissolution test is included in the individual monograph, the test for disintegration is not required. It is determined by USP apparatus. It consists of 6 glass tube each 3 inches long, open

at top and has 10 mesh screens at the bottom end of basket rack. One tablet is placed in each tube and placed in a one litre beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2°C. It moves up and down through a distances of 5 to 6 cm at 28 to 32 cpm.

Uncoated tablet has disintegration time as low as 5 minutes. Majority of tablets has DT of 30 minutes. DT of enteric coated tablet is one hour in simulated gastric fluid and two hours in simulated intestinal fluid. DT for dispersible and soluble tablets is within 3 minutes.

11.8.Wetting time and water absorption ratio:

Wetting time of dosage form is related to with the contact angle. Lower wetting time implies a quicker disintegration of the tablet.

Wetting time:

It is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. To measure wetting time, five circular tissue papers of 10cm diameter are placed in a petridish with a 10cm diameter. 10ml of water containing eosin, a water soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. The water absorption ratio, *R* can be the determined according to the following equation;

$$R = 100 (Wa-Wb) / Wb$$

Where,

Wb; The weight of the tablet before keeping in the petridish.

Wa; The wetted tablet from the petridish is taken and reweighed.

11.9. Analytical methods

Method of analysis for Dissolution

Dissolution Parameters

Table 9. Dissolution parameters

Apparautus	USP Apparatus 2 (paddle)
RPM	75 RPM
Dissolution medium	pH 5.0 Acetate buffer, 900ml
Time	5,10,15(Q),30 and 45 minutes
Sample collection volume	10 mL
Temperature	37.0±0.5°C
λ max	262 nm

Procedure

- Randomly select and weigh six tablets individually. Record the weight of each tablet.
- Run the dissolution test on six tablets by applying the parameters in the table.
- Withdraw sample solution portion of about 10 mL in each dissolution vessel at the specified time point.
- Filter through a 0.45µ PVDF filter by discarding the first 4 mL of the filtrate.
- Sample is analysed by using UV spectrophotometer.

11.10.STABILITY STUDIES:

- The optimized formulation is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics.

11.11.Method of analysis for Assay

Chromatographic parameters

Table 10. Chromatographic parameters for Assay.

Mobile phase	Buffer and acetonitrile (45:55)
Column	X Bridge, C18, 150x4.6mm, 5.0µ Particle Size Manufacturer: Waters, Part no:186003116
Flow rate	1.0mL/min
Sample temperature	Ambient
Column temperature	30°C
Wavelength	220nm
Injection volume	20µL
Run time	10 minutes
Sample retention time	About 4.5 minutes
System suitability	The RSD of Zolmitriptan peak area is NMT 2.0% The USP tailing factor for ambrisentan peak is NMT 2.0from standard preparation. The USP plate count for ambrisentan peak , NLT 3000 from standard preparation.

Chromatographic procedure

- Perform an injection of diluent preparation.
- Perform five (5) replicate injections of the standard preparation.
- USP Tailing factor for Ambrisentan peak is NMT 2.0.
- The relative standard deviation (RSD) of the peak area is not more than 2.0% for Ambrisentan in standard preparation.
- Perform an injection of test solution in duplicates.
- Record the chromatograms and calculate the percentage of Ambrisentan dissolved as per the formula

Percentage Assay

$$= \frac{At}{As} \times \frac{Ws}{100} \times \frac{5}{50} \times \frac{V1}{WT} \times \frac{V3}{V2} \times \frac{P}{100} \times \frac{TW}{LC} \times 100$$

Where,

At = Peak area of ambrisentan from the chromatogram of the assay preparation.

As = Average peak area of ambrisentan from the chromatograms of the standard solution.

Ws = Weight of Ambrisentan WRS taken in mg.

WT =Weight of blend sample taken in mg.

P = Potency of Ambrisentan WRS on as is basis.

LC = Label claim of Ambrisentan tablet, in mg.

V1 =Respective volume of the standard volumetric flask used for sample stock preparation in ml.

V2 =Respective volume of sample pipetted in ml.

V3 =Respective volume of volumetric flask used for sample preparation in mL.

11.12.Content Uniformity

$$= \frac{At}{As} \times \frac{Ws}{100} \times \frac{5}{50} \times \frac{P}{100} \times \frac{V}{LC} \times 100$$

Where,

At = Average peak area of Ambrisentan from the chromatograms of the sample solution.

As = Average peak area of Ambrisentan from the chromatograms of the standard solution

Ws = Weight of Ambrisentan WRS taken in mg.

P = Potency of Zolmitrptan WRS on as is basis.

LC = Label claim of Zolmitriptan tablet, in mg.

V =Respective volume of the standard volumetric flask used for sample preparation in mL.

11.13.Method of Analysis for Impurities and Degradants

Chromatographic parameters

Table 11. Chromatographic parameters for Impurities and degradants.

Mobile phase	Mobile phase A= Buffer Mobile phase B= Acetonitrile		
Column	Sunfire C18,4.6 x 250 mm, 5.0 µm particle size		
Gradient	Time	Mobile phase A (%)	Mobile phase B (%)
	0	50	50
	5	50	50
	15	32	68
	20	25	75
	25	25	75
	30	50	50
	40	50	50
Flow rate	1.0 mL/min		
Sample temperature	Ambient		
Column temperature	35°C		
Wavelength	220nm		
Injection volume	10µL		
Run time	40 minutes		
Sample retention time	About 12 minutes		
Sample preparation	Sample preparations containing Ambrisentan about 1000 µg/mL.		
System suitability	The RSD of Ambrisentan peak area is NMT 5.0% from standard solutions. The theoretical plate count for Ambrisentan is not less than 5000 from standard solution. The tailing factor for Ambrisentan is not more than 2.0 from standard solution		

Chromatographic procedure

- Perform an injection of diluent preparation.
- Perform five (6) replicate injections of the standard preparation.
- The relative standard deviation (RSD) of the peak area is not more than 5.0% for Ambrisentan peak in standard preparation.
- The theoretical plate count for Ambrisentan should not be less than 5000.
- The tailing factor for Ambrisentan should not be more than 2.0.
- Perform an injection of placebo solution.
- Perform an injection of test solution.
- Record the chromatograms and calculate the percentage of impurities and degradants as per the formula.

Calculations

Percentage of known impurity:

$$= \frac{AT1}{AS} \times \frac{WS}{100} \times \frac{5}{100} \times \frac{50}{WT} \times \frac{AW}{LC} \times \frac{P}{100} \times RF \times 100$$

Percentage of Known impurity

$$= \frac{AT2}{AS} \times \frac{WS}{100} \times \frac{5}{100} \times \frac{50}{WT} \times \frac{AW}{LC} \times \frac{P}{100} \times 100$$

Where,

At1 = Peak area of known impurity from the chromatogram of the sample solution.

At2 = Peak area of unknown impurity from the chromatogram of the sample solution.

As = Mean peak area of Ambrisentan from the chromatograms of the standard solution.

Ws = Weight of Ambrisentan WRS taken in mg.

Wt = Weight of Ambrisentan tablets powder taken in mg.

Avg.wt= Average weight of tablets in mg.

P = Potency of Ambrisentan WRS on as is basis.

RF = Response Factor of the known impurity.

LC = Label claim of Ambrisentan tablet, in mg.

12. RESULT AND DISCUSSION

12.1.Pre formulation Studies:

API Characteristics

Bulk density	:	0.291 g / mL
Tapped density	:	0.641 g / mL
Compressibility index	:	54.60
Hausner ratio	:	2.20
PSD by Malvern master Sizer	:	
d10	:	6.7 microns
d50	:	31.4 microns
d90	:	143.3 microns

API Manufacturer : Zhezianghuahai pharmaceutical Co., Ltd

Table .No: 12. API Solubility

Water			0.1N HCL		
Solubility (mg/ml)	Solution Stability (% degradation)		Solubility (mg/ml)	Solution Stability (% degradation)	
	24hrs	48hrs		24hrs	48hrs
0.04670	0.04706	0.04661	0.03948	0.03664	0.03349

pH 3.0 Buffer			pH 4.5 Acetate buffer		
Solubility (mg/ml)	Solution Stability (% degradation)		Solubility (mg/ml)	Solution Stability (% degradation)	
	24hrs	48hrs		24hrs	48hrs
0.01812	0.01732	0.01626	0.10183	0.10182	0.10010

pH 5.0 Acetate buffer			pH 6.8 Phosphate buffer		
Solubility (mg/ml)	Solution Stability (% degradation)		Solubility (mg/ml)	SolutionStability (% degradation)	
	24hrs	48hrs		24hrs	48hrs
0.25395	0.25479	0.25204	3.98	4.00	3.97

pH 8.5 Borate buffer		
Solubility (mg/ml)	Solution Stability (% degradation)	
	24 hrs	48hrs
14.81	14.94	14.80

Based on the above results it is clear that Ambrisentan is less soluble in acidic pH and the solubility increased with increase in pH.

12.2.RLD Characteristics

Letairis®(Ambrisentan tablets, 10 mg)

Lot# SBFW

Exp Date : 09/2018

Manufactured by : Gilead sciences, Inc. Foster City, CA 94404

Pack : Bottle containing 3 tablets stored in a HDPE container with dunnage.

Average Tablet Weight : 148.8 mg

Average thickness : 3.28 mm

Average Hardness : 12 kP

Dissolution

Table 13. Percentage drug dissolved in RLD.

Time (minutes)	Mean % Drug Dissolved
5	65
10	72
15	85
30	91
45	98

12.3.EVALUATION ON PRECOMPRESSION PARAMETERS:

Characteristics of final blend:

Final blend was characterized with various parameters like bulk density, tapped density, angle of repose and loss on drying for each batch and their results were tabulated below

Table 14. Result for bulk density, tapped density, angle of repose and loss on drying for the trial batches.

Particulars	F1	F2	F3	F4	F5	F6	F7
Bulk density (g/mL)	0.56	0.60	0.54	0.56	0.60	0.58	0.61
Tapped density (g/mL)	0.44	0.43	0.34	0.40	0.40	0.39	0.40
Angle of repose Ø	36	39	37	32	33	32	33
% LOD	4.5	5.4	2.9	3.0	2.7	2.8	2.9

Particle Size Distribution

Particle Size Distribution for final blend of the trial batches were performed and the results are tabulated below

Table 15. Particle size distribution results for the final blend of trial batches.

Particulars	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
20	0	0	0	0	0	0	0
40	4	4	2	2	0	2	2
60	14	12	16	14	12	14	16
80	12	10	16	12	14	14	14
100	20	14	18	22	16	18	18
140	13	18	20	22	20	20	22
200	22	26	18	16	20	16	16
pan	15	16	10	12	18	16	12
Total	100	100	100	100	100	100	100

Blend Uniformity

Percentage content of samples from final blend of trial batches were analyzed and the results are tabulated below

Table 16. Results of Blend uniformity samples of final blend of the trial batches

S.No	F6	F7	F8
1	96.7	97.6	98.9
2	100.6	98.7	99.5
3	96.7	97.4	99.9
4	99.8	99.6	99.6
5	99.6	98.9	99.8
6	99.3	99.6	99.1
7	98.1	100.2	98.1
8	100.9	100.1	99.6
9	97.9	100	100.8
10	98.7	99.1	101.2
AVG	**98.8**	**99.1**	**99.65**
Min	96.7	100.2	98.1
Max	100.9	97.4	101.2
%RSD	**1.50**	**1.00**	**0.89**

12.4.Tablet Characterization

Weight Variation:

Weight variation of all the batches were evaluated and the results are tabulated below

Table 17. Results for weight variation of the trial batches

S. No	F1	F2	F3	F4	F5	F6	F7
1	138.4	139.1	139.8	139,4	139.5	140.4	140.1
2	139.9	138.4	136.9	140.1	138.9	138.9	139.8
3	138.6	139.4	139.6	140.5	140.4	139.8	140.1
4	140.0	139.9	140.4	141.0	140.8	140.1	140.6
5	141.4	141.0	140.0	139.5	140.7	140.7	139.7
6	139.9	142.4	140.1	139.1	141.8	138.4	140.1
7	138.6	139.4	140.0	138.4	139.6	138.8	138.1
8	137.5	139.7	139.1	139.0	138.9	19.9	139.2
9	140.3	138.8	137.8	140.1	140.0	138.9	140.0
10	140.1	141.0	138.1	141.0	141.0	140.1	141.0
Avg	139.5	139.9	139.2	139.9	140.2	127.6	139.9
Min	137.5	138.4	136.9	138.4	138.9	19.9	138.1
Max	141.4	142.4	140.4	141.0	141.8	140.7	141.0

Thickness:

Thickness of ten tablets were evaluated from each batch and tabulated in the table below

Table 18. Thickness of tablets of the trial batches.

S.No	F1	F2	F3	F4	F5	F6	F7
1	3.16	3.16	3.15	3.17	3.15	3.15	3.16
2	3.18	3.17	3.16	3.16	3.16	3.16	3.15
3	3.17	3.16	3.14	3.15	3.16	3.17	3.15
4	3.14	3.16	3.14	3.16	3.15	3.16	3.15
5	3.16	3.18	3.13	3.14	3.15	3.15	3.16
6	3.16	3.16	3.14	3.14	3.18	3.16	3.17
7	3.19	3.17	3.14	3.16	3.15	3.17	3.16
8	3.17	3.18	3.15	3.15	3.15	3.16	3.18
9	3.18	3.17	3.12	3.15	3.12	3.14	3.16
10	3.16	3.18	3.15	3.14	3.15	3.14	3.14
Avg	3.17	3.17	3.14	3.15	3.15	3.16	3.16
Min	3.14	3.16	3.12	3.14	3.12	3.14	3.14
Max	3.19	3.18	3.16	3.17	3.18	3.17	3.18

Hardness:

Hardness for ten tablets for the trial batches were evaluated and the observation was tabulated below.

Table 19.Hardness of ten tablets and its average for the trial batches.

S.No	RB-AMB-001	RB-AMB-002	RB-AMB-003	RB-AMB-004	RBSU-AMB-005	RBSU-AMB-006	RB-AMB-007
1	10.00	10.50	10.10	9.81	10.10	11.10	9.20
2	10.10	10.60	10.80	9.80	10.50	10.30	10.00
3	10.20	10.40	10.90	10.00	10.40	10.50	9.80
4	10.00	10.10	10,3	11.00	10.30	10.20	9.60
5	9.60	10.20	9.20	11.20	10.20	9.80	10.00
6	10.10	9.90	10.40	10.70	10.90	10.20	9.40
7	9.90	9.70	9.60	10.90	11.10	10.40	10.40
8	10.40	9.90	9.10	11.00	10.10	10.60	10.20
9	9.60	10.00	9.20	9.90	9.70	10.90	10.80
10	10.80	10.10	9.00	10.40	9.20	10.10	10.90
Avg	10.07	10.14	9.81	10.47	10.25	10.41	10.03
Min	9.60	9.70	9.00	9.80	9.20	9.80	9.20
Max	10.80	10.60	10.90	11.20	11.10	11.10	10.90

Content Uniformity:

Ten tablets from each batch were analysed for content uniformity and the results are tabulated below.

Table 20.Results of percentage content and %RSD of tablets of trial batches.

S. No	F1	F2	F3	F4	F5	F6	F7
1	99.9	96.7	97.9	99.9	99.7	100.3	99.1
2	92.0	97.9	98.9	100.4	100.0	100.5	101.9
3	97.4	99.0	99.8	101.3	100.6	100.2	100.9
4	94.9	101.0	101.7	101.7	100.4	98.9	99.2
5	95.8	103.1	101.1	101.3	99.2	99.4	99.5
6	96.4	104.9	99,4	101.1	100.8	100.4	100.7
7	99.2	100.4	99.2	99.9	100.2	100.9	99.8
8	99.1	100.2	100.6	99.8	100.4	99.6	100.6
9	103.2	99.9	100.4	101.3	100.2	100.4	99.8
10	105.1	99.2	100.1	102.9	100.0	99.9	100.9
AVG	98.3	100.2	100.0	101.0	100.2	100.1	100.2
Min	92.0	96.7	97.9	99.8	99.2	98.9	99.1
Max	105.1	104.9	101.7	102.9	100.8	100.9	101.9

Friability:

Initial weight, final weight and percentage weight loss of tablets from each batch for checking whether they pass the test for friability. And the results are tabulated below.

Table 21.Friability and its parameters for all the batches.

Parameters	F1	F2	F3	F4	F5	F6	F7
Initial Weight (gm)	6.8412	6.7351	6.7638	6.9967	6.8011	6.6509	6.6789
Final Weight (gm)	6.8240	6.7102	6.7449	6.9716	6.7801	6.6499	6.6678
Percentage Weight loss (%)	0.41	0.37	0.28	0.36	0.31	0.01	0.17

Disintegration Time:

Minimum and maximum time taken by the six tablets from each batch was noted and tabulated in the table below

Table 22.Disintegration time of each batch.

Parameters	RB-AMB-001	RB-AMB-002	RB-AMB-003	RB-AMB-004	RBSU-AMB-005	RBSU-AMB-006	RB-AMB-007
Minimum Time (sec)	30	32	1.01	40	42	44	35
Maximum Time (sec)	45	47	1.25	55	53	49	45

12.5.Assay & Water by Kf

Results of assay and moisture content evaluated by karlfischer reagent was tabulated below

Table 23. Assay and water by kf results of the trial batches

Parameters	F1	F2	F3	F4	F5	F6	F7
Assay(%)	96.70	96.80	98.7	97.9	99.2	100.4	100.2
Water by Kf (%)	5.22	5.01	4.97	4.96	4.82	4.68	4.49

12.6.Related substance

The analytical method for related substance was performed and the highest unknown impurity and total impurity values of the respective batches were tabulated below.

Table 24. Highest unknown impurity and total impurities results of the respective batches.

Parameters	F1	F2	F3	F4	F5	F6	F7
Highest Unknown Impurity (%)	0.12	0.17	0.13	0.12	0.13	0.14	0.17
Total Impurities (%)	1.70	1.72	1.07	1.08	1.06	1.10	1.11

12.7.Dissolution[23]

Percentage release of drug was analyzed during 15 minutes of dissolution and the results for the respective batches were tabulated below.

Table 25.results of dissolution data of the trial batches.

Dissolution Media: 0.05 M Acetate Buffer, pH 5.0. USP type II (Paddle) Spec: NLT 80%(Q) in 30 minutes					
Particulars	**5**	**10**	**15**	**30**	**45**
RLD (Letairis)	65.93	72.08	85.45	91.32	98.21
F1	47.21	54.23	59.15	65.89	72.17
F2	51.33	57.74	61.26	67.21	75.32
F3	56.04	61.81	69.07	72.11	79.14
F4	62.62	68.39	72.22	76.64	81.66
F5	69.45	75.17	81.43	88.17	94.21
F6	74.92	79.38	84.64	90.31	99.74
F7	79.22	85.71	91.78	98.36	99.22

And the graphical representation of the batches is shown below.

Fig 8: Graphical representation of Percentage dissolution of the batches F1-F4

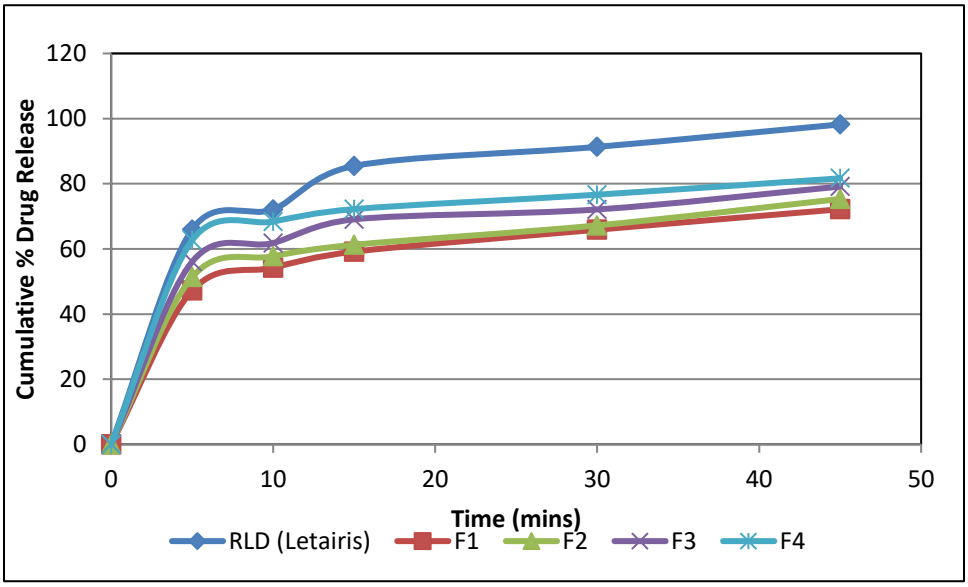
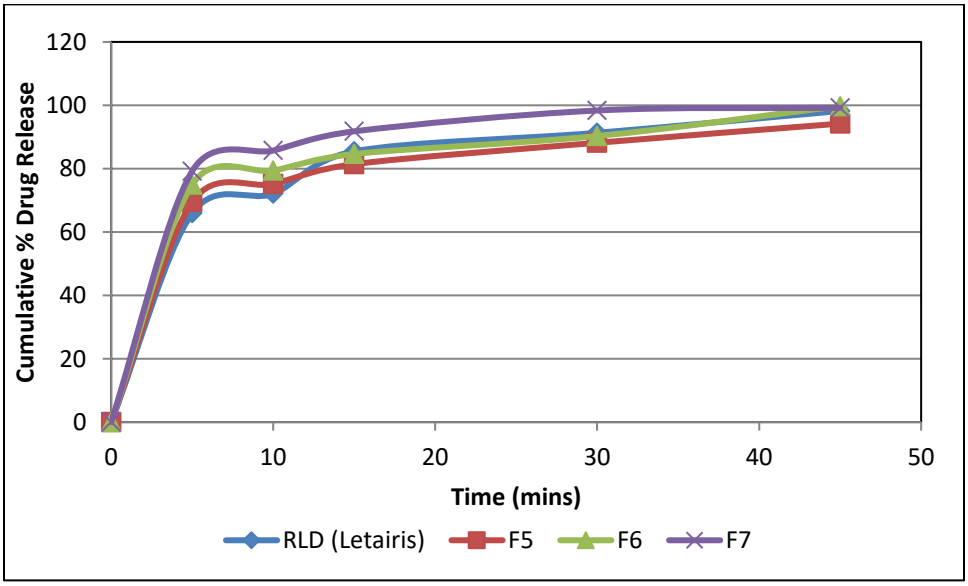


Fig 9: Graphical representation of Percentage dissolution of the batches F5-F7



12.8.Accelerated stability studies[21][22]

30 Tablets with 6g/yard of nylon coil as dunnage is packed in 75cc Heavy Weight HDPE Bottle capped with 33mm Child resistant closure having induction seal liner is loaded along with placebo for analytical use in each condition.

Particulars	Assay	Dissolution	Impurity - D	Any unknown impurity	Total impurity
Specification	**90-110**	**NMT 80% (Q) in 30 minutes**	**NMT 0.5%**	**NMT 0.2%**	**NMT1.0%**
F7 (ACC - 1M)	100.8	98	0.02	0.01	0.06
F7 (ACC - 2M)	99.5	97	0.02	0.01	0.05
F7 (ACC - 3M)	100.2	97	0.03	0.01	0.06

13. SUMMARY AND CONCLUSION

The present study involves formulation and evaluation of immediate release tablets of Ambrisentan. Endeavours with respect to Direct compression method used for formulating tablets was best suitable to achieve 100% results.

Preformulation studies involving organoleptic bulk density, angle of repose, tapped density, compressibility index, hausner ratio, melting point range, pH and solubility were carried out as per USP specifications.

Polymers such as Lactose Monohydrate, Microcrystalline cellulose pH 101(MCC), Croscarmellose sodium (CCS) were utilized in all the trails. All the physical evaluations carried in preformulation studies were carried out on all the three different polymers utilized. All the formulations exhibited values within the acceptable range.

Tablets were evaluated for weight variations, hardness, friability, thickness and Dissolution studies.

Release studies were carried out in pH 5.0 Acetate buffer, for 45 minutes. Evaluated samples for all the Three polymer systems. Results indicated that formulation F7, gave 98.36% release within 30 minutes. Assay was carried out for formulation F7 and was found to be 100.2%.

Remaining formulations gave fluctuating release profiles. The formulation F7 was considered to be better among the trails accomplished.

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